Express Mail No: EV332174669US
Date of Deposit: July 18, 2003

Attorney Docket No: 034615-0022
(HILL-4)

TOPICAL SKIN CARE COMPOSITION CONTAINING PEANUT OIL

FIELD OF THE INVENTION

[01] The invention relates generally to medicated skin treating compositions and more particularly to a cream containing a medicament for the treatment of a hyperpigmented skin condition.

BACKGROUND OF THE INVENTION

[02] Atopic dermatitis (eczema) is an inflammatory disease and the chronic form is typically characterized by dry, thickened, scaling skin. Pruritus (itching) is prominent and most of the cutaneous findings are due to rubbing and scratching. Pigmented lichenified (thickened, scaly skin) pruritic dermatosis is often seen in chronic atopic dermatitis. A key factor in the treatment of this disease is hydration of the skin, along with low- or midpotency topical glucocorticoids (anti-inflammatory).

[03] Allergic contact and irritant contact dermatitis, acne, burns and post-surgical scarring are among some of the other causes of hyperpigmentation. These conditions are localized forms of hyperpigmentation due to epidermal alteration, proliferation of melanocytes, or increased in pigment production in the epidermal layer.

[04] Another common pigmentary condition, melasma or chloasma, primarily affects women in their reproductive years. Dark, mottled (hyperpigmented) patches appear on the face and neck, especially on the cheeks and forehead. Melasma is usually triggered by hormonal activity that is the result of pregnancy or birth control pills. Thus, the condition is known as the "mask of pregnancy". The condition occurs when excess melanin is deposited in the cells of the epidermis and dermis. Melasma can persist for long periods of time and often recurs with subsequent pregnancies. The condition is less common among men, who account for about 10% of all cases.

[05] Standard therapy involves depigmenting, or bleaching, the affected areas of the skin, the use of sunscreens, and avoidance of sunlight. Hydroquinone is the most popular topical depigmenting agent. Concentrations of 5%-10% hydroquinone are very effective, but can be irritating. The chemical stability of hydroquinone formulations is important because hydroquinone is easily oxidized and loses potency. The most commonly used agent usually involves a 16- to 20-week course of therapy, and some therapies can take longer. Tretinoin is another widely used therapy for melasma.

[06] There remains a need in the art for a therapeutic approach that would contain several medicines for the treatment of hyperpigmented lesions in a single composition. Moreover, it would be useful to have a therapeutic carrier, such as a cream, that would improve hydrating effects on human skin. Such a therapeutic carrier would ameliorate the drying effect of the medicaments and thus make the course of treatment more tolerable for the patient, improving patient compliance and thus the therapeutic effectiveness.

SUMMARY OF THE INVENTION

[07] The invention provides a skin care composition, which is a cream base containing peanut oil, for the topical application to the skin. The invention also provides a cream base containing peanut oil, for the topical application of a medicament to the skin. The medicament can be a skin care therapeutic. The invention also provides a process for making the cream base.

[08] In one embodiment, the skin care therapeutic is a medicament for the treatment of hyperpigmented skin conditions, such as melasma. The medicament can be selected from fluocinolone acetonide, hydroquinone or tretinoin, or a combination thereof.

[09] In one embodiment, the invention provides a cream, which includes the inactive ingredients peanut oil, butylated hydroxytoluene, cetyl alcohol, citric acid, glycerin, glycerol stearate, PEG-100 stearate, magnesium aluminum silicate, methyl gluceth-10, methylparaben, propylparaben, purified water, sodium metabisulfite, stearic acid, and stearyl alcohol. As a component of the cream base, peanut oil can be present in an amount of between 1% and 10% of the cream base. Alternatively, the peanut oil can be between about 2% to 9%, or 3% to 8%, or 4% to 7% of the cream base.

[10] The process for making the cream base entails (a) mixing hydrophilic compounds with water to form an aqueous phase; (b) mixing hydrophobic compounds, including the peanut oil, with methylglueth and glycerin to form a hydrophobic (non-aqueous or wax) phase; then (c) mixing the hydrophilic and hydrophobic phases to one another to form a biphasic mixture; and finally (d) adding the emulsifier to the biphasic mixture to form the emulsion. By mixing the emulsifier after the aqueous and non-aqueous phases have been mixed, the result is a smoother-textured cream that disappears upon application to skin, as compared to creams made by processes where the emulsifier was added to the aqueous or non-aqueous phases earlier in the process. Optionally, skin care therapeutic medicaments can be added at step (d) or later.

DETAILED DESCRIPTION OF THE INVENTION

[11] In a preferred embodiment, the composition of the invention contains a cream base for topical application, where the cream base contains peanut oil as a component. In a more preferred embodiment, the composition contains a medicament selected from the group of fluocinolone acetonide, hydroquinone, tretinoin or a combination thereof. For example, each gram of the composition of the invention can contain, as active ingredients, fluocinolone acetonide 0.01% (0.1 mg), hydroquinone 4% (40 mg), and tretinoin 0.05% (0.5 mg). A particularly preferred embodiment is provided in TABLE 1.

TABLE 1

Ingredient	800 g Batch Quantity	Formula
magnesium aluminum silicate NF	24 g	3.00%
butylated hydroxytoluene NF	320 mg	0.04%
cetyl alcohol NF	32 g	4.00%
stearic acid NF	24 g	3.00%
stearyl alcohol NF	32 g	4.00%
methylparaben NF	1.440 g	0.18%
propylparaben NF	160 mg	0.02%
Arlacel® 165 [glycerol stearate and PEG-100 stearate glycerol monostearate]	28 g	3.50%
methyl gluceth-10	32 g	4.00%
glycerin USP	24 g	3.00%
isopropyl myristate	32 g	4.00%
peanut oil NF refined	40 g	5.00%
tretinoin USP	400 mg	0.05%
fluocinolone acetonide USP	80 mg	0.01%
citric acid USP	400 mg	0.05%
hydroquinone USP	32 g	4.00%
sodium metabisulfite NF	1.6 g	0.20%
purified water USP	495.60 g	61.95%
total		100.00%

[12] Fluocinolone acetonide is a synthetic fluorinated corticosteroid for topical dermatological use and is classified therapeutically as an anti-inflammatory. It is a white crystalline powder that is odorless and stable in light. The chemical name for fluocinolone acetonide is (6,11,16)-6,9-difluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]-pregna-1,-4-diene-3,20-dione. The molecular formula is $C_{24}H_{30}F_2O_6$and molecular weight is 452.5. The amount of fluocinolone acetonide in the composition of the invention can be in amount understood by those of skill in the art to be effective. In particular, the amount can be in the range of between 0.005% and 0.02%.

[13] Hydroquinone is classified therapeutically as a depigmenting agent. It is prepared from the reduction of *p*-benzoquinone with sodium bisulfite. It occurs as fine white needles that darken on exposure to air. The chemical name for hydroquinone is 1,4-benzenediol. The molecular formula is $C_6H_6O_2$and molecular weight is 110.11. The amount of fluocinolone

acetonide in the composition of the invention can be in amount understood by those of skill in the art to be effective. In particular, the amount can be in the range of between 0.02% and 0.1%.

[14] Tretinoin is all-*trans*-retinoic acid formed from the oxidation of the aldehyde group of retinene to a carboxyl group. It is highly reactive to light and moisture. Tretinoin is classified therapeutically as a keratolytic. The chemical name for tretinoin is (*all-E*)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid. The molecular formula is $C_{20}H_{28}O_2$and molecular weight is 300.44. The amount of tretinoin in the composition of the invention can be in amount understood by those of skill in the art to be effective. In particular, the amount can be in the range of between 2% and 10%.

[15] The invention also provides a method for making the therapeutic cream. In one embodiment, the therapeutic cream is made using the following steps:

[16] To a 1000 ml beaker add:

water	495.6 g
magnesium aluminum silicate NF	24 g
butylated hydroxytoluene	0.32 g

[17] Heat this mixture to 75-80°C with continued mixing.

[18] To a 400 ml beaker add:

cetyl alcohol	32 g
stearic acid	24 g
stearyl alcohol	32 g
methyl glueth-10	32 g
methylparaben	1.44 g
propylparaben	0.16 g
glycerin	24 g
isopropyl myristate	32 g
peanut oil	40 g

[19] Heat this mixture to 75-80°C and mix until dissolved.

[20] With good agitation transfer the mixture in the 400 ml beaker to the 1000 ml beaker. Allow cooling to begin.

[21] When the temperature reaches 70°C add:

Arlacel® 165	28 g
tretinoin	0.4 g

fluocinolone acetonide 0.08 g

[22] Continue mixing and cooling.

[23] When the temperature reaches 60°C add:

citric acid anhydrous 0.4 g

[24] Continue mixing and cooling.

[25] When the temperature reaches 55°C add:

hydroquinone 32 g

[26] Continue mixing and cooling.

[27] When the temperature reaches 50°C, place the beaker under a counter top homogenizer. Start the homogenizer and continue mixing and cooling.

[28] When the temperature reaches 45°C add:

sodium metabisulfite 1.6 g

[29] Continue mixing and cooling.

[30] Mix the completed batch for at least 30 minutes.

[31] The resulting composition of the invention can be stored at controlled room temperature 68 to 77°F (20 -25°C).

[32] A course of therapy for the composition of the invention containing peanut oil, fluocinolone acetonide, hydroquinone and tretinoin is 8 weeks of topical application.

[33] In another more preferred embodiment, the composition contains tretinoin (0.05%) as the medicament in a cream base containing isopropyl myristate and peanut oil. This embodiment is useful for the treatment of acne. A particularly preferred embodiment is provided in TABLE 2.

TABLE 2

Ingredient	800 g Batch Quantity	Formula
magnesium aluminum silicate NF	24.00 g	3.00%
butylated hydroxytoluene NF	1.60 g	0.20%
cetyl alcohol NF	32.00 g	4.00%
stearic acid NF	24.00 g	3.00%
stearyl alcohol NF	32.00 g	4.00%
methylparaben NF	1.44 g	0.18%
propylparaben NF	0.16 g	0.02%
Arlacel® 165 [glyceryl stearate (and) PEG-100 stearate glycerol monostearate and polyoxyethylene stearate	28.00 g	3.50%
methyl gluceth-10	32.00 g	4.00%
glycerin USP	24.00 g	3.00%
isopropyl myristate NF	32.00 g	4.00%
peanut oil NF refined	40.00 g	5.00%
tretinoin USP	0.40 g	0.05%
citric acid USP anhydrous	0.40 g	0.05%
purified water USP	528.00 g	66.00%
		100.00%

[34] In another more preferred embodiment, the composition contains hydroquinone (4.0%) as the medicament in a cream base containing isopropyl myristate and peanut oil. This embodiment is useful for the treatment of hyperpigmentation or postinflammatory conditions. A particularly preferred embodiment is provided in TABLE 3.

TABLE 3

Ingredient	800 g Batch Quantity	Formula
magnesium aluminum silicate NF	24.000 g	3.00%
butylated hydroxytoluene NF	0.320 g	0.04%
cetyl alcohol NF	32.00 g	4.00%
stearic acid NF	24.00 g	3.00%
stearyl alcohol NF	32.00 g	4.00%
methylparaben NF	1.44 g	0.18%
propylparaben NF	0.16 g	0.02%
Arlacel® 165 [glyceryl stearate (and) PEG-100 stearate glycerol monostearate and polyoxyethylene stearate	28.00 g	3.50%
methyl gluceth-10	32.00 g	4.00%
glycerin USP	24.00 g	3.00%
isopropyl myristate NF	32.00 g	4.00%
peanut oil NF refined	40.00 g	5.00%
citric acid USP anhydrous	0.40 g	0.05%
hydroquinone USP	32.00 g	4.00%
sodium metabisulfite NF	1.60 g	0.20%
purified water USP	527.52 g	65.94%

[35] In the various embodiments, the compositions of the invention are useful for application to any subject in need thereof. The subject can be any vertebrate, especially a mammal, and most especially a human. The composition is amenable to self-application.

[36] The details of one or more embodiments of the invention are set forth in the accompanying description above. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described. Other features, objects, and advantages of the invention will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms include plural referents unless the context clearly

dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All patents and publications cited in this specification are incorporated by reference.

[37] The following EXAMPLE is presented to more fully illustrate the preferred embodiments of the invention. This EXAMPLE should in no way be construed as limiting the scope of the invention, as defined by the appended claims.

EXAMPLE

TEST OF HYDRATING EFFECTS ON HUMAN SKIN BY PEANUT OIL

[38] A test was performed to determine whether pure peanut oil or a corticoid oil formulation and its components could improve hydrating effects on human skin. The measuring was performed using biometrics techniques. Transepidermal water loss (TEWL) was used as a parameter of monitoring the irritant response and capacitance as the parameter of skin hydration. The side effects were also observed in the test. The testing was done by visual grading and by bioengineering techniques on ten healthy subjects (3 male and 7 female, mean age 45±9). The results showed that plain peanut oil, the corticoid oil formulation and the moisturizing vehicle significantly improve skin hydration after one acute application.

[39] Three parameters were selected to evaluate the effects of test formulations:

Clinical visual scoring (scaling; adverse effect-if any):

0 none
1 slight (weak spotty erythema)
2 moderate erythema
3 Severe erythema with edema or palpable infiltration

[40] Transepidermal water loss (TEWL) was assessed by a Tewameter (Tewameter TM 210, Courage, Cologne, Germany, and Academ Inc., Menlo Park, CA). TEWL documents integrity of stratum corneum water barrier function and is a sensitive indicator of skin water barrier alteration. The value of TEWL was expressed as g/m^2 per h.

[41] Skin hydration (*i.e.*, electrical capacitance) was measured by a Corneometer (CM 820, Courage & Khazaka, Cologne, Germany). Capacitance was expressed digitally in arbitrary units (a.u.).

[42] The measurements were conducted in a room with daily ranges of relative humidity (RH) from 55.0 ± 4.6% and temperature from 18.4 ± 0.5°C. These values (RH and °C) were recorded daily. Each subject was rested at least 30 min for acclimation before measurements.

[43] Basal values of TEWL and capacitance were measured on each test site prior to treatment with test materials. The flexor aspects of both forearms of subjects were used for testing. The test sites on the left and right forearm of each subject were randomized. One test site served as normal skin control (without treatment). Other sites were wetted by spraying distilled water (approximately 0.1 ml) over a 3 cm^2 skin surface area. This saturation procedure was repeated on the same site each 5 minutes, for a total of 3 applications. Five minutes post the last application, 0.2 ml of a corticoid oil formulation (Derma-Smoothe/FS®, Hill Dermaceuticals, Sanford, Florida), a moisturizing vehicle, and plain peanut oil were applied to the each pre-designated site (3 cm^2). One site was kept blank control (water saturation only). Thirty minutes later, test sites were gently wiped with paper tissues, and then clinical scores, TEWL, and capacitance were recorded at each test site. These were repeated at 2 and 3 hours.

[44] Statistics were performed using a computer program SigmaStat® (SPSS Science, Chicago, IL). Values of TEWL and capacitance between blank plus water only site and other test site were analyzed with paired *t* test. One-way repeated-measures ANOVA were utilized to evaluate the differences among the plain peanut oil, the corticoid oil formulation and the moisturizing vehicle-treated sites. Levels of significance were marked as follows: *$p<0.05$, **$p<0.01$, ***$p<0.001$.

[45] The results showed that plain peanut oil significantly improved skin hydration after 30 minutes of each single application. There was no statistically difference among plain peanut oil, the corticoid oil formulation and the moisturizing vehicle at any measured time points.

[46] No VS alternation was observed.

[47] Plain peanut oil and the slightly elevated TEWL after 30 min application, but this result was not statistically different.

[48] No adverse effects from test materials were observed.

[49] The results showed that plain peanut oil, the corticoid oil formulation and the moisturizing vehicle significantly improve skin hydration after one acute application. The plain peanut oil, corticoid oil formulation, and moisturizing vehicle all significantly enhanced skin hydration, with no significant differences among them.

[50] These results show that plain peanut oil and moisturizing vehicle can be components of a base of formulation to help restore the normal moisture of skin. Hydrated skins can increase the penetration of applied medicaments or active ingredients, such as fluocinolone acetonide.

[51] The foregoing description has been presented only for the purposes of illustration and is not intended to limit the invention to the precise form disclosed, but by the claims appended hereto.